

3635. (Amended) The method of claim 3231, wherein the boronyl peptidomimetic has an EC<sub>50</sub> for immunosuppression in the  $\mu$ M or greater range.

3736. (Amended) The method of claim 3231, wherein the boronyl peptidomimetic is orally ~~active~~administered orally.

3837. (Amended) A method for modifying glucose metabolism of an animal, comprising administering to the animal a composition comprising a peptidomimetic boronyl inhibitor wherein the peptide to be mimicked is~~including boronyl inhibitor of peptidomimetic of a peptide selected from the group consisting Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.~~

### **REMARKS**

Claims 1-37 constitute the pending claims in the present application. Applicants have cancelled claim 15. Applicants reserve the right to prosecute claims of similar or differing scope as claim 15 in the future. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants acknowledge Examiner's remarks regarding re-numbering of claims 18 through 38 under 37 CFR 1.126. Applicants have re-numbered the claims as 17 through 37 in the present response. Furthermore, Applicants have corrected the dependencies of re-numbered claims 31-36.

2. The abstract of the disclosure is objected to because it is insufficiently detailed as to the identity of the active agents which are to be used. Applicants have amended the abstract to provide added details pertaining to the active agents of the present application. Applicants respectfully request reconsideration and removal of the aforementioned objection in light of the amendment.

3. Applicants acknowledge Examiner's remarks regarding compliance for receiving the benefit of an earlier filing date under 35 U.S.C. 119 and/or 120. Applicants have inserted language at the beginning of the specification to reflect the correct claim to priority and co-pendency of filed applications. Applicants respectfully request reconsideration and removal of the aforementioned objection in light of the amendment.

4. Applicants thank the Examiner for pointing out informalities in the specification. Applicants have made the necessary corrections. Applicants have corrected misspellings on page 18, lines 6 and 9. Applicants respectfully request reconsideration and removal of the aforementioned objection in light of the amendment.

5. Claims 15-28 and 31-37 are rejected under 35 U.S.C. 112, second paragraph, for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have cancelled claim 15. Claims dependent of claim 15 have been amended to reflect proper claim dependency.

- a. To the extent that the rejection is maintained over the remaining claims as amended, however, Applicants have replaced references to "the C $\alpha$  carbon" with "a C $\alpha$  carbon" where appropriate to obviate the rejection. Applicants submit that this amendment does not narrow the scope of the claim;
- b. Applicants have removed the phrases reciting "(such as ...)" from claim 16, 28, and 31. Applicants submit that this amendment does not narrow the scope of the claims as the term merely served an illustrative function;
- c. Applicants note that the variable "X" in cancelled claim 15 was meant to be variable "Z" as would be understood by one with ordinary skill in the art. Applicants have corrected the mistake to the extent it is reflected in the pending claims. Applicants submit that this amendment does not narrow the scope of the claim;
- d. Applicants have made changes to structures in claims 16 and 28 wherein a single bonded monovalent oxygen has been changed to a double bonded divalent oxygen as would be understood by one with ordinary skill in the art. Applicants assert that

one of ordinary skill in the art would have recognized this error, and its obvious correction. Thus, Applicants submit that this change does not narrow the scope of the claim;

- e. Applicants have edited claims 16, 28 and 31 to remove the word “including”, and the phrases “such as pinacol or the like”. Applicants submit that this amendment does not narrow the scope of the claims, as the terms merely served an illustrative function;
- f. As to the rejection of claims 20 and 21 because the “correspondence is not clear between the [phrase] small hydrophobic groups of claims 20 and 21 and the substituents recited in the definitions of  $R_2$  and  $R_3$  in claim 15”, Applicants respectfully traverse the rejection. Applicants point out that the phrase “small hydrophobic groups” has been used in the specification numerous times to refer to lower alkyls or halogens (see page 11 lines 20-21, 23-25; page 16 lines 1-2, 6-8). The term “lower alkyls” is also defined in the specification. Thus, Applicants maintain that there is a sufficient correspondence for the dependence of claims 20 and 21 on claim 15;
- g. Applicants have made a change in the structure represented in the general formula in claim 28 to clarify that  $R_1$  is attached to the amino terminus as would be understood by one with ordinary skill in the art. Applicants assert that one of ordinary skill in the art would have recognized this error, and its obvious correction. Thus, Applicants submit that this change does not narrow the scope of the claim;
- h. Applicants have amended claim 28 to state “active site residue of the targeted protease selected from” instead of “active site residue of the targeted protease, for example”;
- i. Applicants have amended claim 31 by removing references to  $R_5$  and  $R_{61}$  and adding the variables  $R'_7$  and  $R_{62}$  as would be understood by one with ordinary skill in the art. Applicants assert that one of ordinary skill in the art would have

recognized this error, and its obvious correction. Thus, Applicants submit that this change does not narrow the scope of the claim;

- j. Applicants have amended claim 31 by replacing the phrase “represents small hydrophobic groups, preferably lower alkyls, and more preferably methyl” with the phrase “represents lower alkyl or halogen”. Applicants submit that this change does not narrow the scope of the claim; and
- k. Applicants have amended claim 37 by replacing the phrase “including boronyl inhibitor of peptidomimetic of a peptide selected from the group consisting Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala” with the phrase “comprising a peptidomimetic boronyl inhibitor wherein the peptide to be mimicked is selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.” Applicants submit that this change does not narrow the scope of the claim.
- l. Applicants have amended claim 1, 2, 3, and 4 by inserting the structural limitations of claim 15.

Applicants respectfully request reconsideration of this rejection in view of the amendments.

6. Claims 4-7, 13, 15, 16-28 and 30-36 are objected to because of informalities cited in the Office Action. Accordingly, Applicants have amended the claims as follows:

- a. claim 4 now recites “inhibitors of dipeptidylpeptidase IV (DPIV).” instead of “inhibitors dipeptidylpeptidase IV (DPIV)”;

- b. Applicants have inserted a “the” in claim 5 before “dipeptidylpeptidase”; inserted a “the” in claim 6 before “protease”; inserted an “or” in claim 7 before “hyperlipoproteinemia”; changed EC<sub>50</sub> to EC<sub>50</sub> in claims 8, 9, and 10, 33-35; changed the term “tolerance” to “intolerance” in claim 9 as would have been understood by skilled artisan; changed “nm” to “nM” in claim 11; removed all occurrences of the term “group consisting of” or “group consisting”; replaced the term “orally active” with “administered orally” in claims 14 and 36; inserted functional group limitations mistakenly absent in claim 16, but for which there is support in the specification; replaced the term “SH<sub>2</sub>” with “SH” in claims 16, 24, 25, 26, 27, 28; removed the redundant term “wherein” from claim 19; corrected numerical subscripts for

variables in claims 19-22 and 23; corrected the misspelling of “halogenated” in claim 22; corrected grammatical errors in all occurrences of “a alkyl, a alkenyl, a alkynyl”; inserted an “or” before the last functional group limitation in R<sub>3</sub>, R<sub>5</sub> and R<sub>6</sub> in claim 28; and corrected misspelling of “wherein” in claim 31.

c. claim 13 now recites “molecular weight less than” instead of “molecular weights less than”;

d. a semi-colon has been inserted at claim 16, page 55, line 16; claim 24, page 57, line 7; claim 28, line 7; and claim 28, page 61, line 12;

e. a period has been added at the end of claim 16 and 19;

f. in claim 28, misspelling of “independently” has been corrected.

Applicants assert that one of ordinary skill in the art would have recognized these informalities and their obvious corrections, and would not have been confused as to the scope of the claims wherein the informalities were present. Thus, Applicants submit that these corrections do not narrow the scope of any of the claims listed above. Applicants respectfully request reconsideration of the objection in view of the amendments.

7. Claims 22, 24-26, and 28 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully traverse the objection to the extent it is maintained over the amended claims. Applicants have cancelled claim 15. To the extent some of the subject matter of claim 15 appears in amended claim 1, Applicants have corrected the recitations for R<sub>6</sub> which were mistakenly left out, but are supported by the specification. Applicants have also corrected the recitations of functional group possibilities for R<sub>6</sub> in claim 16. Applicants respectfully submit that the claims 24-26 and 28 now have the correct dependency. Claim 22 is objected to because the claim recites R<sub>5</sub> can be a halogenated lower alkyl, which the Office Action maintains is not a possibility embraced by the definition of R<sub>5</sub> in claim 16. Applicants respectfully traverse the objection because an alkyl group is one of the possibilities for R<sub>5</sub> in claim 16. The definition of the term “alkyl” provided in the specification encompasses lower alkyls, and alkyls substituted by halogens. (See Specification on page 20) Thus the recitation of “halogenated lower alkyl” for R<sub>5</sub>

in claim 22 is of a possibility embraced the definition of R<sub>5</sub> in claim 16. Applicants assert that one of ordinary skill in the art would have recognized these errors, and their obvious corrections. Thus, Applicants submit that these changes do not narrow the scope of the claims. Applicants have also changed the dependency of claim 28 from claim 16 to claim 1, 2, 3, or 4. Applicants respectfully request reconsideration of these objections in view of the amendments.

8. Applicants have corrected informalities cited in the Office Action in claim 15, page 54, line 15 to the extent the subject matter of claim 15 appears elsewhere; claim 16, page 55, line 13; and claim 28, page 61, line 9. Applicants assert that one of ordinary skill in the art would have recognized these errors, and their obvious corrections. Thus, Applicants submit that these changes do not narrow the scope of the claims.

9. Claims 2, 30, and 37 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 2, 30 and 37 of co-pending Application No. 09/628,225. Applicants traverse the rejection to the extent it is maintained over the amendments. Applicants have cancelled claims 2, 30 and 37, and claims dependent on them in the co-pending Application No. 09/628,225 such that conflicting claims so are no longer coextensive in scope. Accordingly Applicants respectfully request removal of the rejection.

11. Claims 1-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-67 of co-pending Application No. 09/628,225. The Office Action further stated that “[A]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the ‘225 application anticipate the instant claims.” Applicants traverse the rejection to the extent it is maintained over the amendments. Applicants will address the issue at a later time, should it be maintained.

12. Applicants acknowledge the Examiner’s remarks regarding joint inventorship. Applicants assert that each pending claim was commonly owned at the time of the invention.

13. Claims 1, 3, 5-10, 12, 13, and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by the Deacon et al. article (Diabetes, Vol. 47, pages 764-769) Applicants respectfully traverse this rejection. Applicants assert that the instant application is a continuation of the PCT

Application US99/02294 filed 02/02/99, which in turn claims priority to the US Application 60/073,409, filed on 02/02/98. Deacon et al. was published in 05/98. Applicants assert that the relationship between the instant application and 60/073,409 falls within the condition set forth in MPEP 201.11(a) for receiving the benefit of an earlier filing date: namely, the claimed invention is disclosed in 60/073,409, and sufficiently to comply with the requirements of the first paragraph of 35 U.S.C. 112. Applicants respectfully request reconsideration of this rejection in view of the aforementioned argument.

14. Claims 1-3, 5-16, 20, 21, 25 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application '309. Applicants respectfully traverse the rejection to the extent that it is maintained over the amended claims. Applicants have cancelled claims 1-29. Applicants assert that the new claims are not anticipated by the '309 application. While the '309 application claims DPIV inhibitors, it does not disclose every element of the amended pending claims. The '309 application does not teach or suggest that DPIV inhibitors can be used to modify GLP-1 metabolism. The '309 application discloses that inhibition of DPIV may be useful for immunosuppression, preventing HIV infection of CD4<sup>+</sup> T-cells, preventing metastases, treating psoriatic or arthritic conditions, treating prostate hypertrophy, or suppression of sperm motility. (See page 3 of '309 app) One of ordinary skill in the art reading the '309 application would not have understood that modifying GLP-1 metabolism was a potential use of DPIV inhibitors. As such the instant claims are directed to new and unobvious uses of DPIV inhibitors not disclosed in the 309 application.

The fact that GLP-1 metabolism may have been modified to the same extent in the experiments described in the '309 application is not relevant because, for inherent anticipation of method claims, if a claimed method comprises steps identical to those of a method practiced in the prior art, and the same result would have been achieved in the prior art method, the accidental or unwitting achievement of that result cannot constitute anticipation. *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978). In *Marshall* the PTO board used the *Physician's Desk Reference* (PDR) as a basis for a rejection of the applicant's weight control process. The applicant's process involved anesthetizing certain intestinal nerve ends receptors with oxethazaine. The anesthesia inhibited the release of certain appetite stimulating hormones thereby inhibiting appetite. The PDR had disclosed that oxethazaine inhibits the release of

gastrointestinal hormones, and such inhibition would be useful for treating certain gastrointestinal ailments. In reversing the Board's rejection, the court held that the PDR did not teach the use of the compound as a weight control drug. Addressing the issue of inherency, the court further stated that "[I]f anyone ever lost weight by following the PDR teachings it was an unrecognized accident. An accidental or unwitting duplication of an invention cannot constitute an anticipation." (*id.* 304)

Applicants maintain that *Marshall* is controlling in the instant situation. In *Marshall*, note that the essential question with regards to inherency was not whether oxethazaine had inhibited the release of intestinal hormones in patients prior to the applicant's weight control process, or whether patients had lost weight when oxethazaine was administered to them as an anesthetic. Rather the question was whether the prior reference taught the reader that weight loss can be achieved by using oxathazine. Thus, if the reference does not teach or suggest the claimed process, then the claimed process is new and unobvious in view of the reference.

The instant claims, as amended, are directed to uses of DPIV inhibitors to modify GLP-1 metabolism in an animal. Applicants point out that the MPEP does not foreclose patentability where "new and unobvious uses of old structures and compositions" are present (MPEP 2112.02, original emphasis) Under *Marshall*, "accidental or unwitting duplication of an invention cannot constitute an anticipation." (*Marshall*, 578 F.2d at 304) Thus, to sustain an anticipation by inherency, the '309 application must teach or suggest the benefits of modifying GLP-1 metabolism in a manner that is not accidental or unwitting. One of ordinary skill in the art, having read the '309 application, should be able to achieve therapeutic benefits by modifying GLP-1 metabolism. The '309 application lists six pharmaceutical applications of the DPIV inhibitors discloses therein: (1) immunosuppression, (2) HIV prevention and AIDs treatment, (3) prevention of breast and prostate tumor metastases into the lungs, (4) treatment of dermatological diseases such as psoriasis, (5) suppression of sperm motility to achieve male contraception, and (6) treatment of benign prostate hypertrophy. (See '309 application, p. 3) Applicants point out that none of the six enumerated uses includes therapeutic use for modifying GLP-1 metabolism. The '309 application was not seeking to modify GLP-1 metabolism; it did not monitor the effects the DPIV inhibitors had on GLP-1 metabolism, nor is there any suggestion that GLP-1 metabolism was related to the therapeutic uses enumerated in the application. To the best of

Applicants' knowledge, GLP-1 is not related to the therapeutic uses enumerated in the '309 application. Applicants argue that one of ordinary skill in the art, having read the '309 application, would not have known to use DPIV inhibitors to modify GLP-1 metabolism for therapeutic purposes.

Even if the inhibitors described in the '309 application would have modified GLP-1 metabolism, it is not clear whether appreciable quantities of GLP-1 and its associated metabolic machinery were present in any of the experiments disclosed in the reference. The only biological testing carried out in the '309 application were *in vitro* assays using purified human DPIV. (See '309 application, page 9) There is no indication that any GLP-1 enzyme was even present in the preparation. The experiments disclosed in the '309 application neither show what effects the disclosed inhibitors had on GLP-1 metabolism, nor do they show any beneficial therapeutic uses arising from modifying GLP-1 metabolism. Applicants assert that one of ordinary skill in the art would have been hard pressed to find even a teaching or suggestion that the DPIV inhibitors could achieve beneficial uses by modifying GLP-1 metabolism. Thus, Applicants assert that an inherency rejection cannot be sustained based on the '309 application. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

15. Claims 2, 11, 14-16, 20, 21, and 25 are rejected under 35 U.S.C. 103(a) as being obvious over Deacon et al., as applied against claims 1, 3, 5-10, 12, 13, and 29 above, and further in view of the WO Patent Application '309. Applicants respectfully traverse this rejection because Deacon et al. does not qualify as prior art for reasons stated above. Consequently, the Deacon article is not available art for an objection under 35 U.S.C. 103. The '309 Application alone does not disclose all the elements of the pending invention for reasons set forth above. Applicants respectfully request reconsideration of this rejection.

16. Claims 1-3, 5-24, 26, 27, and 29-37 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application '259. Applicants traverse the rejection to the extent it is maintained over the amended claims. To anticipate a claim, the reference must teach every element of the claim. (MPEP 2131) While the '259 application makes composition of matter claims of DPIV inhibitors, it does not disclose every material element of the claimed subject matter of the instant application because it does not teach or suggest that DPIV inhibitors can be

used to modulate GLP-1 metabolism. In contrast, the instant claims are directed towards methods for modulating GLP-1 metabolism. The '259 application does not teach, suggest, or anticipate a method for using DPIV inhibitors for modulating GLP-1 metabolism. The fact that GLP-1 metabolism may have been modified to the same extent in the experiments described in the '259 application is not relevant because, in inherency anticipation of method claims, if a claimed method comprises steps identical to those of a method practiced in the prior art, and the same result would have been achieved in the prior art method, the accidental or unwitting achievement of that result cannot constitute anticipation. *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978). Any modulation of GLP-1 metabolism in the experiments described in the '259 application would have been an unrecognized accident, and thus cannot constitute inherent anticipation of the instant claims. Therefore, Applicants respectfully request reconsideration of this rejection.

17. Claims 2, 11, 14-24, 26, 27, and 29-37 are rejected under 35 U.S.C. 103(a) as being obvious over Deacon et al. as applied against claims 1, 3, 5-10, 12, 13, and 29 above, and further in view of the WO Patent Application '259. Applicants respectfully traverse this rejection because Deacon et al. does not qualify as prior art for reasons stated above. Consequently, the Deacon article is not available art for an objection under 35 U.S.C. 103. The '259 Application alone does not disclose all the elements of the pending invention for reasons set forth above. Applicants respectfully request reconsideration of this rejection.

18. Claim 4 is rejected under 35 U.S.C. 103(a) as being obvious over Deacon et al. as applied against claims 1, 3, 5-10, 12, 13, and 29 above, and further in view of Efendic et al. Applicants submit that the rejection to the extent it is maintained over the amended claims. Applicants respectfully traverse this rejection. Applicants assert that Deacon et al. does not qualify as prior art for reasons stated above. In the absence of the Deacon article, Efendic et al. does not teach or suggest all the elements of the present claims. Namely, it does not teach the element of administering a DPIV inhibitor to modify GLP-1 metabolism. Thus, there would be no motivation for one of ordinary skill in the art at the time of filing to use DPIV inhibitors for treatment of Type II diabetes. Therefore, Applicants assert that a 35 U.S.C. 103(a) obviousness rejection cannot be sustained. Applicants respectfully request reconsideration of this rejection.

19. Claim 1-3, 5-18, 20, 21, 24, and 29-37 are rejected under 35 U.S.C. 102(a) as being anticipated by WO Patent Application '644. The Office action stated that the '644 Application "teaches administering GLP-2 in combination with a DPP IV inhibitor such as Pro-boro-Pro in order to promote the growth or [sic] small and/or large intestine tissue in a mammal. Treatment of diabetes mellitus is also mentioned. The DPP IV inhibitor prevents proteolysis of GLP-2." The Office Action concluded that "because the same active agents are being administered to the same animals according to the same method steps, inherently metabolism of GLP-1... would be modified to the same extent" in the method of the '644 Application. Applicants traverse the rejection to the extent it is maintained over the amended claims. The MPEP states loss of right to patent under U.S.C. 102 as follows: an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language. (MPEP 706.02) Applicants assert that the instant application is a continuation of the PCT Application US99/02294 filed 02/02/99, which in turn claims priority to the US Application 60/073,409, filed on 02/02/98. The '644 application was published on 18/06/98. Since the priority date of the instant application predates the publication date of the '644 PCT application, the '644 application cannot be used as a basis for the rejection. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

20. Claims 1-17, 20, 21, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Villhauer. The Office action stated that "since the same active agents are being administered to the same animals according to the same method steps, inherently peptide hormone metabolism will be modified to the same extent in the method of Villhauer as is claimed by Applicants." Applicants respectfully traverse the rejection to the extent it is maintained over the amended claims.

Applicants assert that Villhauer does not disclose the compounds in the instant claims as amended. To anticipate a claim, the reference must teach every element of the claim. (Mpep

2131) Applicants have cancelled claim 15. To the extent the subject matter of claim 15 appears in other claims, namely claims 1-4, Applicants have amended the claims such that the compounds in the instant claims are not within the scope of the compounds disclosed by Villhauer. Note in particular that all of Villhauer's compounds contain a prolyl residue wherein the carboxyl moiety has been replaced by a cyano group. In amended claims 1-4 and claims dependent thereon, Applicants have removed a cyano group from being one of the possibilities for W. Therefore, Applicants assert that the compounds in the instant amended claims 1-4, and the claims dependent thereon, are not the same as Villhauer's compounds. Thus, Villhauer does not disclose all the limitations of the instant claims. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

21. Claims 1-4 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by the German Patent 19 61 6486. Applicants traverse the rejection to the extent it is maintained over the amended claims.

Applicants have amended claims 1-4 by adding structural limitations to the claims. Applicants assert that the claims as amended are not anticipated by the '486 patent because the amended claims do not read on the compounds disclosed in the '486 patent. Applicants have also amended claim 29 so that the claim is drawn to boronyl peptidomimetic inhibitors of dipeptidyl peptidase IV. Applicants assert that the '486 patent does not disclose boronyl peptidomimetic inhibitors of dipeptidyl peptidase IV. As such, Applicants submit that the '486 patent fails to anticipate the amended claims 1-4 and 29 because it does not disclose every limitation of the claims. Therefore, Applicants respectfully request reconsideration and removal of the rejection.

### CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Respectfully Submitted,

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